A phase I study of high-dose, intermittent sunitinib in patients with solid tumors

Published: 12-03-2013
Last updated: 23-04-2024

Primary objectives:- To determine the maximum tolerated dose (MTD) of sunitinib when administered once a week or once every two weeks.- To assess the safety and tolerability of sunitinib in a once weekly or once every two weeks dose schedule- To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON44759

Source
ToetsingOnline

Brief title
high-dose, intermittent sunitinib

Condition

- Metastases

Synonym
sunitinib dosing

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Divisie I Beheer BV

Intervention

Keyword: high-dose, intermittent, phase I, sunitinib

Outcome measures

Primary outcome

Primary objectives:

- To determine the maximum tolerated dose (MTD) of sunitinib when administered once a week or once every two weeks.

- To assess the safety and tolerability of sunitinib in a once weekly or once every two weeks dose schedule.

- To assess the influence of food on the pharmacokinetics of sunitinib in this alternative high dose.

Secondary outcome

Secondary objectives:

- To determine the pharmacokinetic (PK) behaviour of the parent compound sunitinib and the primary, active, metabolite SU12662.

- Preliminary assessment of the efficacy of sunitinib intermittent treatment, administered at the MTD determined for each of the time schedules of the study (once weekly or once every two weeks).

- To determine a recommended phase II dose (RP2D) and the optimal dose schedule

- To determine the skin and intratumoral concentration of sunitinib and their correlation with the plasma concentration.

- To assess immune/angiogenesis modulating systemic and local effects such as

MDSC, Tregs and DC subset frequencies and tumor infiltrating leukocytes

Study description

Background summary

Sunitinib, when given in a high-dose, intermittent schedule, may exhibit improved efficacy with an acceptable toxicity profile.

Study objective

Primary objectives:
- To determine the maximum tolerated dose (MTD) of sunitinib when administered once a week or once every two weeks.
- To assess the safety and tolerability of sunitinib in a once weekly or once every two weeks dose schedule
- To assess the influence of food on the pharmacokinetics of sunitinib in this alternative high dose.

Secondary objectives:
- To determine the pharmacokinetic (PK) behaviour of the parent compound sunitinib and the primary, active, metabolite SU12662.
- Preliminary assessment of the efficacy of sunitinib intermittent treatment, administered at the MTD determined for each of the time schedules of the study (once weekly or once every two weeks).
- To determine a recommended phase II dose (RP2D) and the optimal dose schedule
- To determine the skin and intratumoral concentration of sunitinib and their correlation with the plasma concentration.
- To assess immune/angiogenesis modulating systemic and local effects such as MDSC, Tregs and DC subset frequencies and tumor infiltrating leukocytes

Study design

Single center, open-label, phase I dose-finding study of a once weekly and a once every two weeks schedule of high-dose sunitinib.

The initial dose of sunitinib is set at 200 mg once weekly; sunitinib is to be administered p.o. Dose escalation cohorts consist of 3-6 patients per dose level. After determination of the MTD for the once weekly schedule, patients will be enrolled in a once every 2 weeks schedule until the MTD for this schedule is reached. At the MTD level for both schedules, patients will be entered into expansion cohorts; the expansion cohorts will not be opened until at least 42 days after the last patient in the escalation phase received

his/her first study treatment. In the expansion cohorts a minimum of 10 patients will be treated per schedule (once weekly and once every 2 weeks). In the foodcohort (starting after inclusion of the last patients in the expansion cohort) 12 extra patients will be included and treated with the MTD of the once every 2 weeks schedule.

Intervention

A pre-treatment and an on-treatment biopsy will be performed, the second along with a skin biopsy on Day 17, for patients entering both the escalation, the expansion and the food cohort in order to gain more insight into the biological effects of the drug. This biopsy is essential for 5 out of the 10 patients entering the expansion cohort.

Study burden and risks

The most common side effects (observed in at least 10% of patients) in clinical studies with sunitinib were hypertension, fatigue, diarrhea, nausea, vomiting, mucositis, hair and skin changes (yellowish discoloration, red rash, hand-foot skin reaction), taste alteration and loss of appetite.

Literature reports <1% risk of serious complications from the primary tumor biopsies

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
1081 HV Amsterdam
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
1081 HV Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed (by the patient or legally acceptable representative) and dated Informed Consent Form
2. Histological or cytological documentation of incurable locally advanced or metastatic solid malignancy for which no standard therapy exists.
3. Primary tumor or metastatic site must be accessible for biopsy. Patients eligible for the expansion cohort must be willing to undergo tumor biopsies, while tumor biopsy remains optional for patients enrolled in the escalation cohort. Bone metastases are excluded as a biopsy site.
4. Evaluable disease by RECIST version 1.1 criteria (see appendix III; at least 1 target or non-target lesion for dose escalation cohorts; at least 1 target lesion for dose expansion cohort).
5. Patients must have documented radiographic or clinical progressive disease.
6. Age * 18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
8. Normal 12-lead ECG (clinically insignificant abnormalities permitted), and Left Ventricular Ejection Fraction (LVEF) > 50% by multigated acquisition (MUGA) scan or echocardiogram.
9. Normal regulated thyroid function- suppletion or blocking drugs permitted.
10. Urinalysis: no clinically significant abnormalities.
11. Albumin higher than 25 g/L
12. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 14 days prior to screening:
a. Hemoglobin > 5.6 mmol/l
b. Absolute neutrophil count (ANC) >1,5 x 10*9/l
c. Platelet count * 100 x 10*9/l
d. Total bilirubin < 1.5 times the upper limit of normal (ULN)
e. ALT and AST 2.5 x ULN (In case of liver metastases: < 5 x ULN)
f. Serum creatinine <*1.5 x *ULN or Creatinine clearance * 50 ml/min (based on MDRD)
g. PT-INR/PTT < 1.5 x ULN, unless coumarin derivatives are used
h. Activated partial thromboplastin time < 1.25 x ULN (therapeutic anticoagulation therapy is allowed, if this treatment can be interrupted for a biopsy as judged by the treating physician)
Patients with known Gilbert*s disease who have serum bilirubin < *3 x ULN may be enrolled.
Pregnant or breast-feeding subjects: Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. For fertile men or women

of childbearing potential: documented willingness to use a highly effective means of contraception (e.g., hormonal methods [implants, injectables, or combined oral contraceptives], intrauterine devices, sexual abstinence, or vasectomized or surgically sterilized partner). Contraception is necessary for at least 6 months after receiving the study kinase inhibitor.

Exclusion criteria

1. Evidence of a significant uncontrolled concomitant disease, such as cardiovascular disease (including stroke, New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to screening, unstable arrhythmia, clinically significant valvular heart disease and unstable angina); nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture.
2. Prior radiotherapy in the abdomen or in the lungs or in more than 3 vertebrae in the spine (Less than 3 vertebrae are considered a small radiation field and eligibility will be decided on an individual basis from the PI)
3. Poorly controlled hypertension despite adequate blood pressure medication. Blood pressure must be *160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 2 separate measurements.
4. Seizure disorders requiring anticonvulsant therapy.
5. Major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1, without complete recovery.
6. Known active bacterial, viral, fungal, mycobacterial, or other infection (including HIV and atypical mycobacterial disease, but excluding fungal infection of the nail beds.)
7. Known hypersensitivity to sunitinib or to its excipients.
8. Presence of any significant central nervous system or psychiatric disorder(s) that would interfere with the patient*s compliance.
9. Drug or alcohol abuse.
10. Females who are pregnant or breast-feeding.
11. Any evidence of a disease or condition that might affect compliance with the protocol or interpretation of the study results or render the patient at high risk from treatment complications.
12. Unwillingness or inability to comply with study and follow-up procedures.
13. No chemotherapy, radiotherapy, or biologic therapy within the previous 4 weeks; no nitrosoureas or mitomycin C within the previous 6 weeks; no investigational agents within the previous 4 weeks.
14. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.
15. Untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control);
16. Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:
* Presence of evaluable or measurable disease outside the CNS
* Radiographic demonstration of improvement upon completion of

CNS-directed therapy and no evidence of interim progression between completion of CNS-directed therapy and the screening radiographic study
* Completion of radiotherapy * 8 weeks prior to the screening radiographic study
* Discontinuation of corticosteroids and anticonvulsants * 4 weeks prior to the screening radiographic study.
Note: Prior sunitinib therapy does not constitute an exclusion criterion.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-07-2013
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	sutent
Generic name:	sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	12-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005756-41-NL
CCMO	NL43122.029.13